Practitioner's Docket No. 051058-034000 (formerly NUCL 006/01-US) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	PACHUK et al.	Confirmation No.:	3823
Application No.:	10/560,377	Group No.:	1648
Filed:	06/19/2006	Examiner:	PENG, Bo
For:	CONSERVED HBV AND HCV SEQUENCES USEFUL FOR GENE SILENCING		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Dear Sir:

This is filed in response to the Final Office Action mailed August 17, 2010 in the above-noted U.S. patent application.

Amendments to the Specification begin on **page 2** of this paper.
The **Listing of the Claims** begins on **page 3** of this paper.
Remarks begin on **page 5** of this paper.

Amendments to the Specification:

Please replace the specification filed December 12, 2005 with the substitute specification submitted herewith – the replacement is a copy of parent PCT application PCT/US2004/019229 as filed. The substitute specification adds no new matter.

Please replace the first paragraph of the substitute specification submitted herewith with the following replacement paragraph:

CROSS REFERENCE TO RELATED ~~APPLICATION~~ APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. §371 of International Patent Application PCT/US2004/019229, filed June 10, 2004, which claims the priority of U.S. Provisional Application Serial No. 60/478,076, filed June 12, 2003, each of which is hereby incorporated by reference in its entirety.

Listing of the Claims:

The following listing of the claims is to replace all previous listings of the claims.

1-62. (CANCELLED)

63. (PREVIOUSLY PRESENTED) A method for inhibiting expression of a polynucleotide sequence of hepatitis B virus in an *in vivo* mammalian cell comprising administering to said cell a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10; wherein U is substituted for T.

64. (PREVIOUSLY PRESENTED) The method of claim 63, wherein at least two of said double-stranded RNA effector molecules are administered to the same mammalian cell.

65. (PREVIOUSLY PRESENTED) The method of claim 64, wherein said at least two double-stranded RNA effector molecules comprise an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within SEQ ID NO:3 and SEQ ID NO:10.

66. (PREVIOUSLY PRESENTED) The method of claim 65, wherein said administering is accomplished by providing one or more expression vectors capable of expressing in said mammalian cell said at least two double-stranded RNA effector molecules.

67. (PREVIOUSLY PRESENTED) The method of claim 66, wherein said one or more expression vectors further comprise a promoter selected from an RNA polymerase I promoter, an RNA polymerase II promoter, a T7 polymerase promoter, an SP6 polymerase promoter, an RNA polymerase III promoter, a tRNA promoter, and a mitochondrial promoter, said promoter operably linked to a sequence encoding at least one of said double-stranded RNA effector molecules.

68-77. (CANCELLED)

78. (PREVIOUSLY PRESENTED) A composition for inhibiting the expression of a polynucleotide sequence of hepatitis B virus in an *in vivo* mammalian cell comprising a double-stranded RNA effector molecule, comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10; wherein U is substituted for T.

79. (PREVIOUSLY PRESENTED) The composition of claim 78 comprising at least two double-stranded RNA effector molecules wherein said effector molecules comprise an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within SEQ ID NO:3 and SEQ ID NO:10.

80-97. (CANCELLED)

98. (WITHDRAWN) The method of claim 63, wherein said double-stranded RNA effector molecule comprises a sequence selected from the group consisting of SEQ ID NOs 18-22 where U is substituted for T.

99. (WITHDRAWN) The method of claim 98 wherein expression of said double-stranded RNA effector molecule in an HBV cell culture transfection assay mediates at least 87% inhibition of HBsAg level relative to control lacking said effector molecule.

100. (WITHDRAWN) The composition of claim 78 wherein said double-stranded RNA effector molecule comprises a sequence selected from the group consisting of SEQ ID NOs 18-22 where U is substituted for T.

101. (WITHDRAWN) The composition of claim 100 wherein expression of said double-stranded RNA effector molecule in an HBV cell culture transfection assay mediates at least 87% inhibition of HBsAg level relative to control lacking said effector molecule.

REMARKS

Claims 63-67, and 78-79 are pending. Claims 98-101 are withdrawn as being directed to a non-elected invention. No claim amendments are made herewith.

Specification- New Matter Rejections

Applicant cancels all subject matter considered by the Examiner in the Office Action issued August 17, 2010 to be "new matter" and provides herewith a copy of the PCT specification (from PCT/US04/019229) to serve as a substitute specification. Specifically, Applicants hereby cancel the amendments to the specification specified in the amendments filed a) with the National Phase entry application on December 12, 2005, and b) in the preliminary amendment filed June 19, 2006. Kindly enter the parent PCT specification submitted here as a substitute specification, and enter the amendment to the first paragraph specified in the "Amendments to the Specification" provided herein to recite the proper priority information.

Rejections under 35 USC 102

1. Claims 63 and 78 are rejected under 35 USC 102(b) as being anticipated by US Patent No. 5,843,770 (Ill et al.).

Applicants disagree and note that the Ill et al. reference cited by the Examiner generally relates to the introduction of double-stranded DNA (i.e., a plasmid) that provides the expression of single-stranded anti-sense molecules, while the invention as presently claimed is directed to methods and compositions employing double-stranded RNA molecules. Regarding the structure of the dsRNA recited in the instant claims, Claim 63 recites the limitation "comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation." Ill et al. does not teach double-stranded RNA molecules, nor does Ill et al. teach RNAs having 19 contiguous nucleotides present in a double-stranded conformation. Neither the antisense molecules taught by Ill et al., nor Ill et al.'s SEQ ID NO:1 in particular, have any such double-stranded character.

SEQ ID NO: 1 described in Ill et al. is a *single-stranded* 587 nucleotide fragment excised from the genome of HBV, as evidenced by information in the Sequence Listing that recites:

"(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 587 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: **single**
(D) TOPOLOGY: linear."
(Emphasis added)

It is clear from the sequence listing that SEQ ID NO: 1 is not a double-stranded RNA effector molecule having a region of at least 19 contiguous nucleotides in a double-stranded conformation as presently required by the pending claims. Thus, Ill et al. does not teach or suggest the dsRNA molecules or their administration as presently claimed.

The Office Action states the following at page 5, lines, 3-6:

> "Forming "a double-stranded conformation" is an inherent property of SEQ ID NO:1. Since SEQ ID NO: 1 of the prior art is the antisense sequence of SEQ ID NO: 10 of the instant application, it must have the ability to form "a double-stranded conformation" like the instant SEQ ID NO:1."

Applicants respectfully disagree. Applicants submit that while the antisense HBV RNA taught by Ill et al. may form a double-stranded structure upon hybridization to its cognate HBV sense RNA, the antisense RNA that Ill et al. administers or expresses is not double-stranded. This is evidenced by Ill et al.'s own characterization, i.e., the Sequence Listing as noted above. That is, Ill et al. does not perform the required step of administering a dsRNA to an HBV-infected cell.

The Examiner appears to be arguing that any RNA possesses the inherent ability to form a double-stranded conformation and that SEQ ID NO. 1 of Ill et al. would therefore have the ability to form a dsRNA having characteristics of the dsRNA molecule recited in the claims. The possibility that the antisense RNA forms a hybrid with the HBV RNA in a cell, or the ability to do so, is not relevant where Ill et al. administers or expresses only the antisense strand.

The Office Action states:

> "Forming "in a double-stranded conformation" of a RNA is an inherent property of RNA. In other words, an RNA would form "in a double-stranded conformation," when there are proper CG or AU base pars (sic) within its own sequence or with a target sequence"

Applicants disagree. The Office Action has taken part of the specification's definition of "dsRNA" referring to at least 2 base-paired nucleotides out of context and apparently disregards

the requirement of the claims that there be at least 19 contiguous nucleotides in a double-stranded conformation. Although antisense RNA may have the inherent ability to form a double-stranded conformation with its cognate sense RNA, the Examiner has not provided any evidence that Ill et al.'s SEQ ID NO: 1, by itself and as administered, comprises a dsRNA molecule that satisfies the limitations of the invention as presently claimed. The Examiner has not indicated any regions of SEQ ID NO:1 that have internal sequence complementarity such that an RNA molecule having a region of at least 19 contiguous nucleotides in a double-stranded conformation would necessarily be present in the administered or expressed molecule. Applicants note that inherency is not established on the basis of possibility or probability - the allegedly inherent characteristic (i.e., at least 19 contiguous nucleotides of double-strandedness) must be present to inherently anticipate the claimed invention. (see e.g., *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); and MPEP §2112). Applicants respectfully request that the Examiner specifically indicate where Ill et al. teaches a double-stranded RNA effector molecule (or administration thereof) having any stretch of at least 19 contiguous nucleotides in a double-stranded conformation.

Further, the invention as presently claimed requires that the "double-stranded conformation includes at least 19 nucleotides from ***within*** a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10" (Emphasis added). Given that SEQ ID NO: 1 of Ill et al. is 587 base pairs in length, it clearly does not fall ***within*** the sequence of SEQ ID NO: 3 or 10. Further, there is no basis provided in the Office Action that an antisense RNA of Ill et al.'s SEQ ID NO: 1 would inherently have internal self-complementarity of at least 19 contiguous nucleotides within sequence corresponding to either of SEQ ID NO: 3 or 10. Applicants respectfully request that the Examiner point out where such sequence lies.

Applicant submits that the Ill et al. reference does not anticipate the invention as presently claimed and respectfully requests reconsideration and withdrawal of the rejection under §102 over the Ill et al. reference.

2. Claims 63 and 78 are rejected under 35 USC 102(b) as being anticipated by US Patent Application US20020155124 (now US Patent No. 6,680,059; Sallberg et al.). The Office Action

cites the Sallberg et al. reference as teaching a nucleic acid based antigen (SEQ ID NO: 14) comprising "a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence." Applicant respectfully disagrees.

Sallberg et al. does not teach or even suggest a dsRNA molecule having at least 19 contiguous nucleotides in a double-stranded conformation. Since Sallberg et al. does not provide any teachings that are relevant to the claimed invention, Sallberg et al. does not anticipate the invention as presently claimed.

The Office Action states at page 6, lines 6-14:

> "**As defined by the specification Para [0049], the claimed dsRNA molecule can be in the form of a double-stranded DNA**, DNA/RNA hybrid, or a single stranded RNA. Given that the HBV nucleic acid-based antigen comprising SEQ ID NO: 14 and its fragments of the prior art **is in the form of double-stranded DNA, and they can form DNA/RNA hybrids, or mRNA (a single stranded RNA)** ***in vivo***, the HBV nucleic acid-based antigens of the prior art meet the structural limitation of the claimed dsRNA effector molecules. Thus, Sallberg's method of using the HBV nucleic acid-based antigen comprising SEQ ID NO: 14 and its fragments for inhibiting HBV *in vivo* anticipate the instant Claims 63 and 78." (Emphases added)

The Examiner appears to be basing the rejection on a section in paragraph [0049] of the specification that defines a dsRNA molecule to encompass a double-stranded DNA. Applicants disagree and respectfully request that the Examiner point out the specific lines in paragraph [0049] that form a basis for such a conclusion. Applicants note that paragraph [0049], lines 25-30 recites the following:

> "By "dsRNA" is meant a nucleic acid containing a region of two or more nucleotides that are in a double-stranded conformation. It is envisioned that the conserved viral sequences of the invention may be utilized in any of the many compositions known in the art or subsequently developed **which act through a dsRNA-mediated gene silencing or RNAi mechanism**." (Emphasis added)

The definition of dsRNA as noted above indicates that the dsRNA acts through a dsRNA-mediated gene silencing or RNAi mechanism. Double-stranded DNA is neither a dsRNA (i.e., to permit dsRNA-mediated gene silencing) nor does double-stranded DNA mediate RNAi. It is clear from this definition that, contrary to the Examiner's argument, double-stranded DNA is not encompassed by the term dsRNA effector molecule.

The Examiner appears to be operating under the assumption that SEQ ID NO: 14 and its fragments, which the Examiner admits are in the form of double-stranded DNA, is capable of forming DNA/RNA hybrids, or mRNA (a single stranded RNA) *in vivo*. Based on this apparent assumption, the Examiner asserts that the HBV nucleic acid-based antigens of the Sallberg et al. reference meet the structural limitations of the dsRNA effector molecules recited in the claims.

Applicants disagree. Whether the double-stranded DNA of Sallberg et al. **can** form DNA/RNA hybrids is irrelevant to the rejection, since Sallberg et al. does not teach or suggest that such DNA/RNA hybrids are administered or formed, particularly *in vivo*. One of skill in the art would understand that double-stranded DNA does not typically generate a DNA/RNA hybrid *in vivo*. Similarly, while Applicants agree that under the proper conditions, double-stranded DNA can be transcribed *in vivo* to produce a single-stranded mRNA, Applicants submit that such mRNAs do not have the double-stranded character required of the dsRNA recited in the instant claims. Further, Sallberg et al. does not teach or suggest the use of dsRNA effector molecules that act through an RNAi mechanism or a dsRNA-mediated gene silencing mechanism as required by effector molecules satisfying the definition of the term "dsRNA." Applicants submit that Sallberg et al. does not anticipate the invention as presently claimed.

Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection based on the Sallberg reference.

Rejections under 35 USC 103

Claims 63-67, 78 and 79 are rejected as being obvious in view of Ill et al., Sallberg et al., and McCaffrey et al. The teachings of Ill et al. and Sallberg et al. as cited by the Examiner are described herein above. McCaffrey et al. is cited as teaching RNAi to inhibit production of HBV replicative intermediates both in cell culture and in mice. The Office Action concludes that the combination of the three cited references teaches the invention as presently claimed. Applicant respectfully disagrees.

The Ill et al. and Sallberg et al. references do not teach double stranded RNA comprising at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T as required by the instant claims. There is nothing in Ill et al. to indicate that SEQ ID NO: 1 or single-stranded antisense RNAs Ill et al. teach form a dsRNA molecule as defined by

the instant claims. Similarly, the double-stranded DNAs of Sallberg et al. are not dsRNA molecules that anticipate the invention as presently claimed (see the preceding discussion). There is nothing in Ill et al. or Sallberg et al. that teaches or suggests the use of dsRNA molecules that act through a dsRNA-mediated gene silencing method as required by the definition of dsRNA as discussed above.

Applicants note that while McCaffrey et al. may teach double stranded RNA in the context of HBV inhibition, the reference does not teach the use of a dsRNA comprising at least 19 contiguous base pairs of nucleotide sequence in a double-stranded conformation from *within a sequence* selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10. That is, McCaffrey et al. does not teach targeting conserved region 3 as disclosed in the instant specification (SEQ ID NO: 3 corresponds to conserved region 3, and SEQ ID NO: 10 is a sub-sequence within SEQ ID NO: 3).

In view of the above, Applicants submit that the proposed combination of Ill et al., Sallberg et al. and McCaffrey et al. fails to teach all elements of the invention claimed in claims 63-67, 78, and 79. As such, the cited combination fails to render the claimed invention obvious. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

In view of the above, all issues raised in the Office Action have been addressed herein. Reconsideration of the claims is respectfully requested.

Should any other fees be associated with this submission, Applicants authorize the Commissioner to charge such fees to Nixon Peabody Deposit Account No. 50-0850, making reference to Docket No. 051058-034000. Any overpayments should also be credited to said Deposit Account.

Respectfully submitted,

Date: November 17, 2010

/Mark J. FitzGerald/
Mark J. FitzGerald (Reg. No. 45,928)
Attorney for Applicant
NIXON PEABODY LLP
100 Summer Street
Boston, MA 02110
(617) 345-1058